REMARKS

Claims 1, 3-6, 14, 17-21 and 23-28 are pending in this application. Claim 17 has been canceled without prejudice, claims 1, 4, 5-6, 18-20 and 23 have been amended, and new claims 29-37 have been added. After claim amendments, additions and cancellations herein, claims 1, 3-6, 14, 18-21 and 23-37 will be pending in this application.

This Amendment is being filed along with a Request for Continued Examination and a Petition for Two-Month Extension of Time in response to the final Office Action dated November 3, 2003 in connection with U.S. Patent Application No. 09/121,017. Following that final Office Action, Applicants mailed on April 30, 2004 a Notice of Appeal and a Petition for Three-Month Extension of Time, which were received by the USPTO on May 3, 2004.

In the November 3, 2003 final Office Action, the Examiner reminded Applicants that the substitute specification filed March 29, 2002 has not been entered. Applicants thank the Examiner for the reminder. Applicants note the Examiner's comments in the November 13, 2002 Office Action that the changes made to the specification that formed the basis for the substitute specification (i.e., the change of the term "sugar chain" to "sugar chains") constituted the addition of new matter since the specification as filed did not recite the plural form, regardless of mistranslation of the Japanese priority application. Applicants also note the Examiner's comments that the specification as filed contained inherent support for the recitations of "one or more" and "plurality of" in conjunction with the term "sugar chains". As such, there is no need for the substitute specification, and Applicants no longer request its entry.

In the November 3, 2003 final Office Action, the Examiner rejected claims 1, 3-6, 14, 17-21 and 23-28 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Examiner also rejected claims 1, 3-6, 14, 17-21, and 23-28 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner further rejected claims 1, 3-6, 14, 17-21, and 23-28 under 35 U.S.C. §102(e) as being entirely anticipated by U.S. Patent No. 5,489,699 (Saunders et al.).

Response to § 112 Rejections in U.S. Patent Application No. 09/121,017

In the November 3, 2003 Office Action, the Examiner again rejected claims 1, 3-6, 14, 17-21 and 23-28 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Examiner's rejections and Applicants' response to each are set out below.

- In claims 1 and 19-20, the term "the residual activity" is not clear, and in claims 6 and 23, the term "the activity" is unclear, because (1) it is not clear what kind of "activity" is intended (i.e., heparin binding activity or other protein activity, such as growth promoting activity); (2) it is not clear what is baseline activity that the "residual activity" is compared against, and it is not clear whether the protein that serves as the comparison standard is glycosylated or not; and (3) it is not clear if there is some process or treatment that the protein is subjected to (such as a destabilizing process) to determine how much "residual activity" remains.

In response, Applicants have amended claims 1, 19 and 20 (note that claim 16 was previously canceled) to delete the word "residual" (Applicants have also deleted this word from claim 18, although the examiner did not reject this claim).

In addition, with respect to the meaning of the term "activity" in claims 1, 6, 19-20 and 23, Applicants direct the Examiner to Figure 5 and Test Example 2 which give the definition and clarity of the term "activity" as DNA synthesis promoting activity. For example, Figure 5 shows an FGF-1α derived from E. coli (Fig. 5B) losing radioactivity without heparin at some concentration range, while S/FGF-1α-II of Applicants (Fig. 5A) does not. Furthermore, Test Example 2 in the specification describes how the cell cycle of HUVEC (human umbilical cord-derived vascular endothelial cell) stops even in the presence of 15% serum if growth factors such as FGF are lacking. The amount of radioactivity taken up into DNA was regarded as indicating the amount of the newly synthesized DNA, i.e., the DNA synthesis promoting activity. Thus, the meaning of the term "activity" as DNA synthesis promoting activity is understandable based upon a review of the specification. However, to the extent necessary and should the Examiner require it, Applicants are prepared to amend the claims to clarify this term.

- In claims 1, 16, 18-20 and 23, the third and fourth members of the Markush grouping of sugar chains are not properly recited, as it is not clear how, in reciting an "O-linked (or N-linked)

sugar chain combined with a sulfated polysaccharide or glycosaminoglycan", these are combined. The Examiner cannot find a description of such combination in the disclosure.

In response, Applicants have deleted from claims 1, 18-20 and 23 (note that claim 16 was previously canceled) the terms in the third and fourth members of the Markush grouping of sugar chains relating to the combination of an O-linked or N-linked sugar chain with a sulfated polysaccharide or glycosaminoglycan.

- In claims 4, 16 and 18-20, "through a peptide" or "containing a peptide sequence" are not clear, as it is not clear how the peptide is structurally related to the heparin binding protein.

In response, Applicants have also amended claims 4 and 18-20 (note that claim 16 was previously canceled) to clearly state how the peptide is structurally related to the heparin binding protein. Amended claims 4, 18 and 19 now read, "wherein at least one (the) sugar chain(s) is (are) covalently bonded to a peptide, which is covalently bonded to the heparin-binding protein and to which the sugar chain(s) is (are) added." Amended claim 20 now reads "wherein the heparin-binding protein is covalently bonded to the peptide sequence to which the at least one sugar chain is added".

- In claim 6, "near one of the ends" is a relative term that is not defined in the claim or specification, and it is also not clear if this addition must be at a residue within a heparin binding protein or can be at a residue of a peptide fused thereto. The Examiner stated that the claims and disclosure give no direction as to how many residues away from the end can one add the sugar chain and still be considered near to one of the ends, and it is not clear if this addition must be at a residue within the heparin binding protein, or if it can be at a residue of a peptide fused thereto.

In response, Applicants delete the term "or at a site near one of the ends" from claim 6.

The Examiner also rejected claims 1, 3-6, 14, 17-21, and 23-28 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner stated that the previous addition of the term "combined with a sulfated polysaccharide or glycosaminoglycan" in each independent claim within the third and fourth members of the Markush group of sugar chains (these were originally recited as "an O-linked sugar chain, an N-linked sugar chain") constitutes addition of new matter, as nothing in the originally filed

disclosure pointed to a combination of an O- or N-linked sugar chain with a sulfated polysaccharide or glycosaminoglycan.

In response, Applicants have deleted from claims 1, 18, 19, 20 and 23 (claim 16 was previously canceled) the terms in the third and fourth members of the Markush grouping of sugar chains relating to the combination of an O-linked or N-linked sugar chain with a sulfated polysaccharide or glycosaminoglycan and also deleted the words "and combinations thereof" following the four elements of the Markush grouping of sugar chains. No combinations of the four Markush elements are now recited in these claims. In addition, Applicants have also deleted the reference to the N-linked sugar chain from claims 1, 18, 19, 20 and 23.

The Examiner also stated that claim 23 contains new matter by reciting "wherein the activity of the heparin binding protein is greater than the activity of the unmodified protein". The Examiner stated that he cannot find any literal or inherent support for this phrase, but that, from page 5 and the examples, it appears that the Applicants have disclosed that the modified proteins have improved stability over the unmodified proteins. In response, Applicants have amended claim 23 to delete reference to "the activity of the heparin binding protein is greater than the activity of the unmodified protein." Claim 23 now recites "wherein the heparin-binding protein has improved stability over the unmodified proteins", as suggested by the Examiner. Furthermore, Applicants have added new claim 29 to further define the instances in which the stability of the claimed heparin-binding protein is improved over that of the unmodified proteins. Support for these amendments can be found at page 5 of the specification.

Applicants believe that these claim amendments overcome the Examiner's claim rejections under § 112, and Applicants request that these rejections be withdrawn.

In addition, in order to further clarify the claims, Applicants have amended all claims 1, 3-6, 14, 18-21 and 23-28 that were pending in this application in order to clarify their terms. Previously, the claims used the term "heparin-binding protein" in both the preamble and body of the claims. Applicants have now amended the independent claims to refer to "A functionalized heparin-binding protein" that comprises "a heparin-binding protein and at least one sugar chain

covalently bonded thereto", and Applicants have amended the dependent claims to refer to the "functionalized heparin-binding protein" of the base claim. These amendments are not being made to narrow the scope of the invention but merely to clarify the language of the claims, and Applicants request that these amendments be entered.

Response to Prior Art Rejections in U.S. Patent Application No. 09/121,017

The Examiner rejected claims 1, 3-6, 14, 17-21 and 23-28 under 35 U.S.C. § 102(e) as being entirely anticipated by Saunders et al. The Examiner stated that Saunders et al. disclose heparin binding proteins, such as those of the FGF family, which are expressed as fusion proteins, such that the FGF is fused to a portion of a core peptide known to undergo glycosylation (sugar addition). The sugars which are added to this core peptide include the glycosaminoglycan heparin sulfate. The Examiner stated that such fusion proteins have increased stability (residual activity) and increased binding activity for the growth factor receptor. The Examiner stated that, therefore, all the features of these claims are anticipated.

In response, Applicants assert that Saunders et al. does not teach all the elements as disclosed in the amended independent claims of 1, 18-20, and 23. Claims 1, 18-20, and 23 have been amended to include the limitation of part (a) of claim 5 and now recite, "wherein the heparin-binding protein comprises the amino acid sequence of SEQ ID NO: 1, 17, 19, 21, 23 or 29." Saunders et al. does not explicitly or inherently disclose a heparin-binding protein comprising any of the amino acid sequences of SEQ ID NO: 1, 17, 19, 21, 23 or 29 of the presently claimed invention, and Applicants assert that this was acknowledged by the Examiner in his rejection of only part (b) of claim 5. Claim 5 has also been amended to delete from part (b) the verbiage regarding the deletion, substitution, addition or modification of at least one amino acid from the amino acid sequences named. Thus, Saunders et al. does not teach every element of the claimed invention and therefore, does not anticipate amended claims 1, 18-20, and 23, as well as dependent claims 3-6 and 24-28. In addition, claim 25 has been amended to change its dependency from previously canceled claim 16 to claim 23. Accordingly, Applicants believe that the Examiner's § 102(e) rejections have been overcome, and Applicants request that this rejection be withdrawn.

Applicants have added new claims 30-37 and similarly assert that Saunders et al. does not teach or suggest all the elements as disclosed in these new claims. Claims 30-37 recite that the heparin-binding protein comprises (a) a proteoglycan core protein or a part thereof, to which the sugar chain is bonded, and (b) a specific amino acid sequence, wherein the amino acid sequence is chosen from the group consisting of: the portion of the amino acid sequence of SEQ ID NO: 1 starting with Asn at number 88 and ending with Asp at number 221, the portion of the amino acid sequence of SEQ ID NO: 17 starting with Asn at number 67 and ending with Asp at number 200, the portion of the amino acid sequence of SEQ ID NO: 19 starting with Asn at number 67 and ending with Asp at number 200, the portion of the amino acid sequence of SEQ ID NO: 21 starting with Asn at number 121 and ending with Asp at number 254, and the portion of the amino acid sequence of SEQ ID NO: 23 starting with Asn at number 148 and ending with Asp at number 281. Saunders et al. does not disclose (or suggest) a heparin-binding protein comprising any of the specific amino acid sequence portions from SEQ ID NOS: 1, 17, 19, 21 or 23. Thus, Saunders et al. does not anticipate amended claims 30-37 (or render them obvious).

It should be noted that the addition of new claims 30-37 and the reference therein to the specific 134 amino acid sequence portion from one of SEQ ID NOS: 1, 17, 19, 21 and 23 does not constitute the addition of new matter, as specific support for the limitations of this claim can be found in the specification. As is clear from the specification, the claimed functionalized heparin-binding protein is a fused protein, the two portions of which, at the DNA level, come from different origins and are ligated together before expression. See, for example, at page 9, line 10-12, which states that "a cDNA coding for a peptide to which a sugar chain can be added is ligated to a cDNA coding for a heparin-binding protein."

The first portion of the functionalized heparin-binding protein, the cDNA coding for a peptide to which a sugar chain can be added is, as recited in claim 30, a proteoglycan core protein or a part thereof to which the sugar chain is bonded. This portion of the functionalized protein is variable. For example, in SEQ ID NO: 1, the variable portion is 87 amino acids long (amino acid nos. 1-87); in SEQ ID NOS: 17 and 19, the variable portion is 66 amino acids long (amino acid nos. 1-66); in SEQ ID NO: 21, the variable portion is 120 amino acids long (amino acid nos. 1-120); and in SEQ ID NO: 23, the variable portion is 147 amino acids long (amino

acid nos. 1-147). All these variable sequences are proteoglycan core protein or a part thereof (human syndecan-4), and each comprises a Ser-Gly repeat sequence, which is required to anchor the sulfated polysaccharide or the like (see, page 9, line 21 - page 10, line 4).

The second portion of the functionalized heparin-binding protein, cDNA coding for a heparin-binding protein, is, as recited in claim 30, a specific amino acid sequence portion. This portion of the functionalized protein is not variable even though it is chosen from a Markush grouping. In all of SEQ ID NOS: 1, 17, 19, 21 and 23, this non-variable sequence portion is made up of the same terminal 134 amino acids, beginning with Asn and ending with Asp, which are identical in all the named sequences, and these are the specific amino acid sequence portions listed in the Markush grouping of claim 30. Namely, in SEQ ID NO: 1, this non-variable portion is amino acid nos. 88-221; in SEQ ID NOS: 17 and 19, this non-variable portion is amino acid nos. 67-200; in SEQ ID NO: 21, this non-variable portion is amino acid nos. 121-254; and in SEQ ID NO: 23, this non-variable portion is amino acid nos. 148-281. This sequence of 134 amino acids is well known in the art, as discussed below.

For example, in Jaye et al., *Science*, Vol. 233, pp. 541-45 (August 1986), Figure 2 shows the entire nucleotide sequence of human β-ECGF and the deduced amino acid sequence. Using bovine ECGF as an example, Jaye et al. discussed a polypeptide that is 21 amino acids shorter at the amino terminus (see page 542, center column, immediately above Figure 2), which is the sequence referenced throughout the specification as FGF-1α. The truncated α-form of this sequence begins with Asn-Tyr-Lys-Lys-Pro (NYKKP), as recited in new claim 30.

Similarly, in Imamura, et al., *Science*, Vol. 249, pp. 1567-70 (September 1990), the difference between the α-form and the β-form of HBGF-1 is more clearly disclosed. In these proteins, Met-Ala (MA) was added at the front of each, as is customary for the convenience of the expression if *Escherichia coli*. As is commonly known, alanine is the smallest amino acid and perhaps inhibits activity the least, and it was thus selected as the most appropriate amino acid to separate the methionine from the desired protein. As such, it is noted that the native protein, the β-form of the protein, is 21 amino acids longer at the amino acid terminus than the truncated α-form.

As shown in the Jaye et al. and Imamura et al. references from *Science*, this partial amino acid sequence consisting of 134 amino acids (Asn-Tyr-Lys-Lys-Pro ... Asp, corresponding to, e.g., amino acids nos. 88-221 in SEQ ID NO. 1, and others recited in new claim 30) was well known in the art at the time of Applicants' invention. This sequence of 134 amino acids is referenced throughout the specification as FGF-1α. In Example 1 of the instant specification, at page 18, the inventors wrote, "using human FGF-1 cDNA as a template" without naming the sequence, because such a cDNA is registered in a gene bank (as stated at page 9, line 16-20). Accordingly, the disclosure in the specification was considered unnecessary, as it is clear that the FGF-1α activity, the object of the present invention, is available only with this specific portion.

Thus, the division of the amino acid sequence of SEQ ID NOS: 1, 17, 19, 21 and 23 for inclusion in the claim of a variable proteoglycan core protein portion to which the sugar chain is bonded and a non-variable specific amino acid sequence portion consisting of, for example with respect to SEQ ID NO: 1, only the part starting with Ala at number 87 and ending with Asp at number 221, is clearly supported in the specification, and the recitation in the new claims of this specific sub-sequence should not be considered the addition of new matter

Conclusion

In view of the amendments and remarks set forth herewith, applicants believe that all claims are now in condition for allowance. A favorable action on the merits is earnestly solicited.

Respectfully Submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Morey B. Wildes
Reg. No. 36,968

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940